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Alimentary Tract

Maintaining standard volumes, efficacy and safety, of fecal microbiota transplantation for *C. difficile* infection during the COVID-19 pandemic: A prospective cohort study

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ABSTRACT

Background: Fecal microbiota transplantation (FMT) can be a life-saving treatment against recurrent *Clostridioides difficile* infection (CDI). It is therefore necessary to maintain this procedure available for these patients during the COVID-19 pandemic while keeping high efficacy and safety standards.

Aims: To report outcomes of a FMT service that has adapted its operational workflow during COVID-19 pandemic to continue offering FMT to patients with CDI.

Methods: All patients with CDI referred to our center for FMT during pandemic were prospectively included. Each step of the FMT working protocol was adapted with specific security measures to prevent the transmission of SARS-CoV-2.

Results: Of 26 patients evaluated for FMT, 21 were treated for recurrent or refractory CDI. Eighteen patients completed the 8-week follow-up, and no one recurred after FMT. Follow-up is ongoing in 3 patients, although in all of them diarrhea disappeared after the first procedure. No serious adverse events were reported. Two patients had also COVID-19-related pneumonia, and were cured both from CDI and COVID-19.

Conclusion: This is the first report to show that it is possible to maintain standard volumes, efficacy and safety of FMT for recurrent CDI during the COVID-19 pandemic, by adopting specific changes in the operational workflow.

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1. Introduction

The pandemic of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has suddenly changed the routine organization of health-care facilities worldwide. Hospitals have been forced to rearrange their structures and reduce drastically elective activities, both to face the medical burden of the pandemic and to avoid the circulation and potential infection of patients.

Beyond these general reasons, gastroenterology units had to re-organize their activities in many areas [1–3].

Fecal microbiota transplantation (FMT) has recently emerged as a life-saving and cost-effective treatment for recurrent *Clostridioides difficile* infection (rCDI) [4]. In specific cases (e.g. severe CDI) [5] the priority of FMT is comparable to that of other urgent endoscopic procedures, and should be considered non-postponable during the COVID-19 time as well. However, although FMT has become an extremely safe and organized procedure over years [6,7], the risk of a potential transmission of SARS-CoV-2 through feces has raised the need for updated working protocols [8–10].

However, this pandemic raises several concerns on the risks of potential SARS-CoV-2 transmission associated with FMT, and poses

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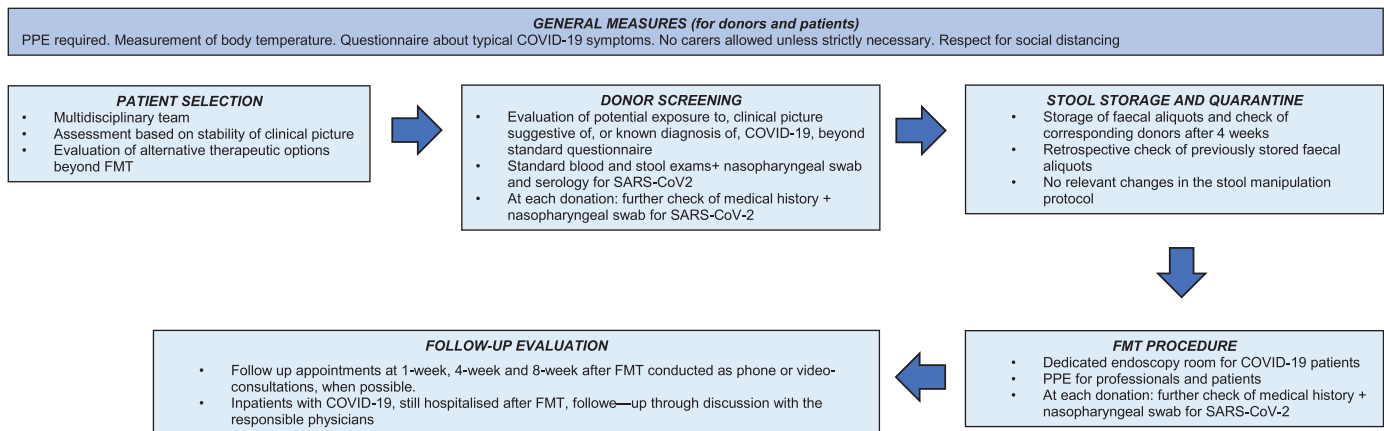


Fig. 1. reorganization of the FMT workflow.

new challenges on the whole organization of FMT services, from selection of patients and donors to feces manipulation and delivery. As there is a considerable risk to continue dealing with COVID-19 in the mid-long term, an international expert panel has recently updated the previous guidelines [6,7] on the general organization of FMT services based on the current pandemic risk [11]. This effort has become strictly necessary, as some FMT centers had suspended the active recruitment of new donors until updated FMT protocols were available.

In recent months, several hospitals had to triage different procedures based on precise clinical priorities. Our hospital hosts a high-volume FMT service that performs on average 120 FMT procedures per year and is a referral for patients with rCDI from the whole Italy. To guarantee the availability of this life-saving therapeutic option despite the restrictions imposed by the COVID-19 pandemic, we have adapted our routine practice by adopting specific security measures for each step of the working protocol, anticipating the implementation of most of the recently published recommendations [11].

We herein report outcomes of a FMT service that has adapted its operational workflow during COVID-19 pandemic, in order to continue offering FMT to patients with rCDI.

2. Materials and methods

2.1. Study design and enrolled subjects

This is a single-center, prospective observational cohort study, performed at the Fondazione Policlinico Universitario “A. Gemelli” IRCCS in Rome, reported following STROBE guidelines [12]. All FMT donors and all patients with rCDI who have been referred to our center for FMT between March 7 and July 10, 2020, have been considered for inclusion. All enrolled subjects provided their written informed consent. The study protocol was approved by the local ethics committee.

2.2. reorganization of the FMT workflow

The reorganization of our FMT workflow is summarized in Fig. 1.

Beyond the application of general measures recommended by the health department of our hospital, we have adapted each step of our FMT working protocol, including patient selection, donor recruitment, manipulation of feces, FMT procedure and patient follow-up, with specific security measures to prevent the transmission of SARS-CoV-2.

2.2.1. General measures

Before entering the hospital, all subjects (donors and patients) were obliged to wear adequate personal protection equipment (PPE), including plastic gloves, and at least surgical masks. Body temperature was measured at entrance and subjects were questioned about typical COVID-19 symptoms, including fever, cough, sore throat, body aches, malaise, anosmia [13]. Carers were not allowed to enter, unless strictly necessary. Respect for social distancing was guaranteed in waiting rooms and transit places, and visit timeslots were adequately separated, to avoid crowding of patients.

2.2.2. Patient selection

Indications to FMT were assessed by physicians on a case-by-case basis, depending on the stability of the patient clinical picture, the severity of CDI, other comorbidities, effectiveness of previous therapies. Patients with suspect or known diagnosis of COVID-19 were specifically evaluated by multidisciplinary team (including a gastroenterologist and an infectious disease physician).

In all cases, alternative treatments with other approved therapies (e.g. vancomycin or fidaxomicin) were considered if FMT was clinically postponable.

When possible, evaluation visits or multidisciplinary discussions were done virtually.

2.2.3. Donor recruitment and screening

All steps of our standard donor screening protocol (evaluation of clinical history, laboratory testing, and checks on the day of donation) were adapted to minimize the risk of COVID-19 infection of donors and recipients. These additional measures were based on the recommendations from the U.S. Food and Drug Administration, the Italian National Transplant center and the recently published suggestions from an international FMT expert panel [8,9,11,14].

When possible, the initial evaluation of potential donor candidates was performed by phone or video consultation. In specific cases (e.g. physician decision, or donor desire) the visit was carried out in the FMT center.

The clinical questionnaire was expanded with specific additional questions, including: known diagnosis of laboratory-confirmed SARS-CoV-2 infection; close exposure to subjects with suspected or proven infection; appearance of specific symptoms (including fever, cough, dyspnea, chills, anosmia or ageusia, sore throat, muscle pain) not explainable by alternative diagnosis, within the previous 30 days [13]; active work as healthcare professional. In case of positivity to at least one of these items, the candidate donor was excluded.

Then, all potential donors underwent laboratory exams, that included, beyond standard testing [7], also a nasopharyngeal swab

and RT-PCR assay for SARS-CoV-2 [8,9,11,14]. From June 1, specific IgG and IgM serology for COVID-19 have been added into the panel of laboratory exams for donor screening.

Finally, the day of each donation donors were assessed again for known diagnosis of, exposure to, and typical symptoms of COVID-19 not explainable by another diagnosis, and repeated nasopharyngeal swab and RT-PCR assay for SARS-CoV-2 (and, from June 1, also a rapid IgM and IgG assay for COVID-19).

After 8 weeks from the initial screening, donors who kept providing feces repeated clinical assessment and the complete panel of laboratory testing.

2.2.4. Quarantine, stool manipulation and storage

All donated stools were manipulated as FMT aliquots, frozen and stored at -80°C and finally quarantined for 4 weeks. After that time frame, corresponding donors were assessed again for diagnosis of, symptoms of, or exposure to, COVID-19.

This check was also done retrospectively for stored fecal samples collected before the start of the COVID-19 pandemic. If this further check was negative, collected feces were ready for use, otherwise were discarded.

Protocols for stool manipulation and storage were not significantly modified, as we were already following international guidelines that recommend strict security measures [7]. If FMT was repeated, aliquots from the same donor of the first procedure were used.

2.2.5. FMT procedures in outpatients and inpatients without COVID-19

Colonoscopic FMT is the preferred route of delivery in our center. FMT for rCDI was included among the non-postponable endoscopic procedures at our center, and we followed the ESGE guidelines on the use of PPE for endoscopic procedures during COVID-19 [15].

Before entering the endoscopy room, all patients were checked for body temperature, investigated about symptoms, and given a surgical mask to be worn for the whole permanence in the endoscopy service. Social distance (2 m) was kept in waiting rooms, and chaperons were not allowed to stop within these areas.

All procedures were performed by colonoscopy, using pediatric colonoscopes and carbon dioxide insufflation, by expert endoscopists (G.I., S.B., G.C.). Operators were always provided with FFP2 or FFP3 masks, gowns and face shields, and were educated on the proper methods for wearing PPE. The fecal infusion procedure followed recommendations from international guidelines [6]. Patients were called 24 h after the procedure to assess for any short-term adverse events or procedural complications.

2.2.6. FMT procedures in hospitalized patients with COVID-19

A separate building of our hospital was restructured to host patients with COVID-19 (COVID-19 hospital). FMT procedures of inpatients with COVID-19 were performed in a dedicated endoscopy room of the COVID-19 hospital, with negative pressure and its own equipment. The day of the procedure, the frozen aliquot was brought by the physician and nurse of the FMT center to the endoscopy room in a cooler, and then thawed there at room temperature. Each aliquot release was documented using the forms of our FMT center. FMT procedures were performed as described before, with anesthesiological support.

2.2.7. Follow-up of patients

Follow up appointments at 1-week, 4-week and 8-week follow-up were conducted as phone or video-consultations, when possible. Follow-up visits of patients who had received FMT prior to the COVID-19 pandemic were carried out in a telemedicine regimen, too, if the clinical picture was stable.

Table 1

Characteristics of treated patients and of infusion procedures.

Number of patients	21
Male/female	7/14
Mean age (range)	74 (20–93)
Number (mean; range) of recurrences	3 (1–4)
Refractory	2
In/outpatients	7/14
Number of patients with COVID19 infection	2
Number (mean; range) of fecal infusions	1 (1–3)
frozen/fresh material	26/0
fecal dosage (grams) (mean; range)	57 (40–60)
PMC at endoscopy	4
Follow-up at	
8 weeks:	
- Response	18
- Unresponse	0
- Ongoing	3

PMC = pseudomembranous colitis.

Inpatients with COVID-19 who were still hospitalized after FMT were followed-up through discussion with the responsible physicians at the COVID-19 hospital. After discharge, patients were followed-up with video-consultation whenever possible.

2.3. Collection of data and outcomes

The following baseline data were recorded for each patient: age; sex; comorbidities assessed with the Charlson Comorbidity Index [16]; number of previous *C. difficile* recurrences; severity of CDI, according to the definitions of the European Society of Clinical Microbiology and Infectious Diseases [17]; known diagnosis of, typical symptoms of, or exposure to, COVID-19.

The number and characteristics of enrolled donors and of stored fecal aliquots was recorded.

The following outcomes were assessed for each patient: resolution of CDI at 8 weeks; development of any serious adverse events (including new diagnosis of COVID-19).

2.4. Statistical analysis

For continuous variables, data were expressed as means with SDs and medians with interquartile ranges. For categorical variables, data were expressed as numbers and percentages. Statistical analyses were carried out with an online calculator (<http://www.graphpad.com/quickcalcs/>) and with Microsoft Excel for Mac (Microsoft Excel. Redmond, Washington: Microsoft, 2011).

3. Results

3.1. Demographics and clinical characteristics of patients

Between March 2020 and July 2020, 26 patients with recurrent or refractory CDI were newly evaluated for FMT.

All patients were first evaluated through video-consultation. In three patients coming from other Italian regions, an alternative treatment option – specifically, tapered vancomycin – was chosen after multidisciplinary discussion, based on their stable clinical picture and the difficulties in reaching the center. Two patients refused the procedure, as they were afraid of entering the hospital, and were treated with tapered vancomycin as alternative.

Overall, 21 patients were treated with FMT for recurrent or refractory CDI ($F=14$, $M=7$; mean age 74 years). Seven were inpatients, and two of them had COVID-19-related pneumonia and CDI refractory to standard antibiotic regimens (vancomycin and fidaxomicin). Also, four inpatients presented with a severe clinical picture, while other patients had mild CDI. The mean number of re-

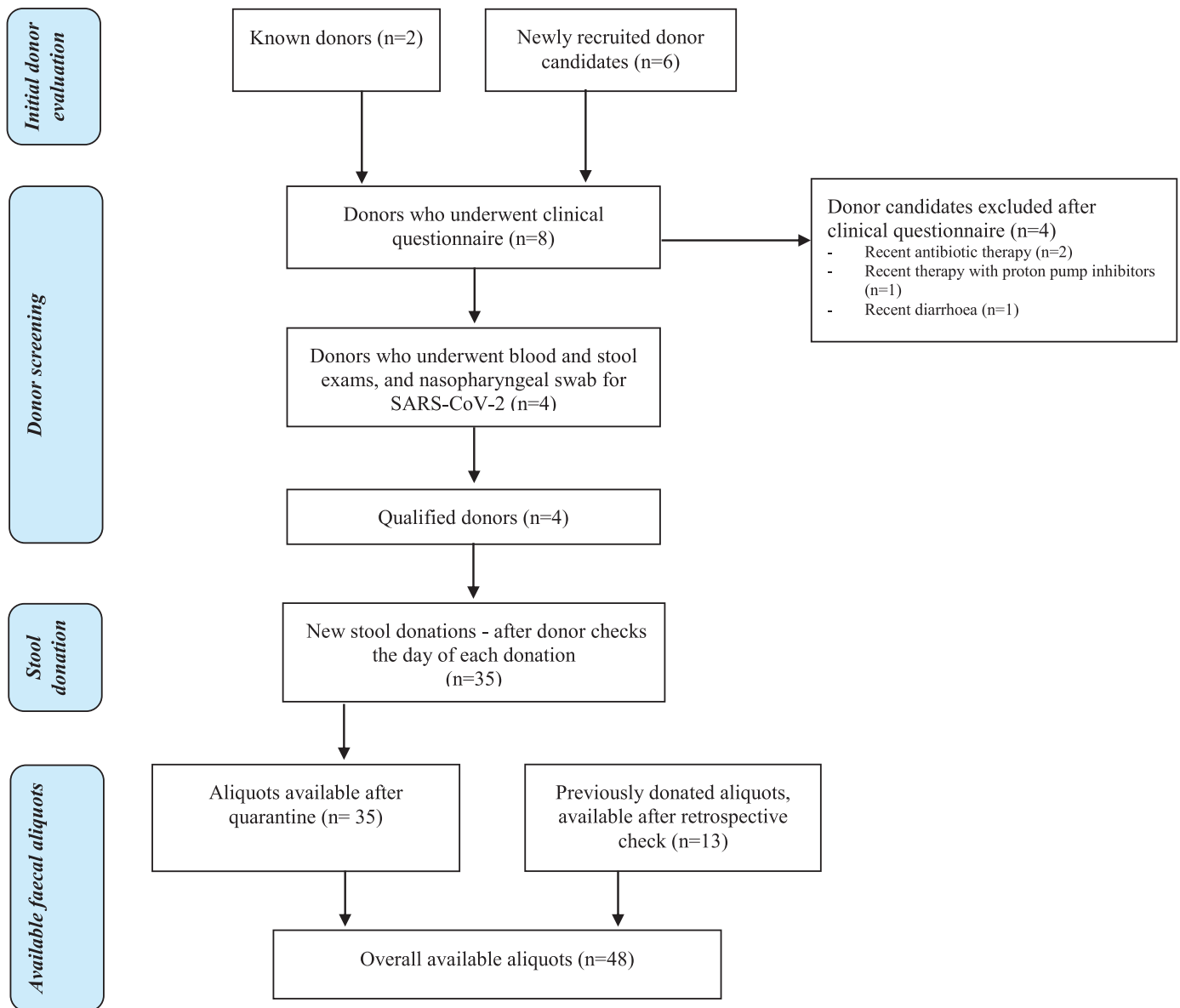


Fig. 2. Workflow of donated stools at our FMT center during the COVID-19 pandemic.

currences was 3 (range 1–4). Other demographics and clinical characteristics of patients are detailed in Table 1.

Finally, 15 patients, who had received FMT between January and February 2020 before the start of COVID-19 outbreak in Italy, were followed-up by phone and video consultation during the study period. As their clinical picture was stable and no one experienced recurrence of symptoms, no in person visits and/or repeat of FMT were necessary.

3.2. Donors and collected fecal samples

At the beginning of the COVID-19 outbreak, 13 fecal samples were already available in our stool bank, and none of the corresponding donors had symptoms and/or diagnosis of, or exposure to, COVID-19.

In the study period, we enrolled two new donors, and repeated complete screening in two known donors. None of them refused to come to the hospital to undergo screening and donate feces. In all subjects, the clinical interview was conducted through video-consultation.

All donors were negative to nasopharyngeal swab for SARS-CoV-2, and none was diagnosed with COVID-19 during the study period. Details of donor workflow during pandemic is showed in Fig. 2.

Overall, 35 fecal aliquots were newly collected and stored in the study period. Of them, 9 were ready for use at the end of April 2020, 17 at the end of May 2020, and 9 at the end of June 2020.

3.3. FMT characteristics and outcomes

Overall, 26 fecal infusions were performed during the study period, as all patients received at least one infusion and three patients were treated with a sequential FMT protocol (one because of pseudomembranous colitis suddenly found at first procedure, and two because of severe clinical picture, receiving, respectively, two and three fecal infusions). The mean Boston Bowel Preparation Scale score was 4. All patients received frozen feces from universal anonymous donors (13 from samples already stored before pandemic, and 13 from newly collected samples). A mean (\pm SD) of 57 ± 6.7 gs of feces were infused during each procedure.

At 10 August 2020, 18 patients have completed the 8-week follow-up, and no one recurred after FMT. Follow-up is ongoing in the remaining six patients, although in all of them diarrhea disappeared after the first procedure. None of the patients experienced serious adverse events, and no new COVID-19 infections were diagnosed.

3.4. FMT in patients with COVID-19

In the study period, two inpatients (respectively, 93 and 80 year old) with COVID-19 developed CDI during hospitalization. None of them had a critical clinical picture at the time of enrollment. Both of them were first treated with pulsed vancomycin for the first infection and, after recurrence (which occurred within one week after the end of vancomycin), were treated first with vancomycin and then, for persistence of diarrhea, with fidaxomicin. However, both patients were refractory also to fidaxomicin and then, after multidisciplinary discussion, were treated with FMT (single infusion), without any adverse event. At follow-up, CDI was cured, as well as COVID-19, in both of them.

4. Discussion

To our best knowledge, this is the first prospective report of the routine activities and outcomes of a FMT referral center during the COVID-19 pandemic. Through specific changes in our working protocol, we were able to maintain volumes and outcomes of the pre-COVID-19 era and to guarantee a high safety level.

Potentially SARS-CoV-2 can be transmitted from human to human, with different risk levels, during each step of FMT, including donor recruitment and screening (because of the circulation of potential donors in the hospital), manipulation, storage and release of donor stools (because of the potential fecal-oral transmission from donors to healthcare professionals), until to the infusion of feces itself through different routes (with potential donor-to-patient, patient-to-healthcare professional, or donor-to-healthcare professional transmission) and the follow-up visits (for the circulation of patients in the hospital).

To prevent the transmission of SARS-CoV-2, we have adapted our FMT working protocols based on the most recent evidence and on available recommendations [8,9,11]. Moreover, our model is in line with recently published guidelines on the reorganization of FMT services during the COVID-19 pandemic, although they were not yet available at the beginning of our study [14].

Most changes, including general safety practices, preference of videoconsultation over visits in person, virtual multidisciplinary meetings and security measures during procedures, were common to the rearrangement models of other fields, such as IBD clinics or endoscopy services [1,2]. Moreover, due to the unique nature of FMT, we had to modify specifically the donor screening to avoid as much as possible the transmission of SARS-CoV-2 by feces. These changes included the evaluation of symptoms of, or exposure to, COVID-19, a further assessment through nasopharyngeal swab, and a 30-day quarantine of stored feces.

Direct stool testing for SARS-CoV-2 has been advocated as the safest way to prevent FMT-related transmission of COVID-19 and has been preliminarily applied to FMT donor screening [10,18]. The direct stool testing approach has already been suggested in the latest consensus conference on stool banks to avoid transmission of bacterial pathogens [7], and we are planning to include it in our protocol, once validated testing tools will be available. However, our model, despite the limited sample size, was highly safe, as no new COVID-19 infections were diagnosed after FMT, and should be acknowledged as a reliable approach in the absence of adequate stool testings.

Through this reorganization model, we were able to maintain the standard performances of our FMT center, as both patient volumes and cure rates were similar to those of the pre-COVID-19 era. However, as the follow-up of some patients is still ongoing and the sample is limited, our findings should be interpreted with caution.

Finally, a further captivating insight is given by the positive outcomes of the two patients with COVID-19 and rCDI, which were both cured successfully. Beyond the known efficacy on rCDI [4,19], it is also possible to speculate that FMT may have also contributed, through the restoration of healthy gut microbiota and modulation of the gut-lung axis [20] – which has been suggested to participate the pathogenesis of COVID-19 [21], to a more favourable immunologic environment and, consequently, to a milder clinical evolution of COVID-19.

Further studies to identify the pathogenic and therapeutic role of gut microbiota in COVID-19 infection are needed to confirm this hypothesis.

In conclusion, the adaptation of the FMT working protocol to prevent transmission of SARS-CoV-2 has allowed our center to maintain volumes and outcomes of the pre-COVID-19 era in patients with rCDI. Although this model could be promising, its reproducibility and its outcomes in other FMT centres remains to be assessed.

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Declaration of Competing Interests

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